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# Surrogate species selection for assessing potential adverse environmental impacts of genetically engineered insect-resistant plants on non-target organisms

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**Keywords:** biosafety, environmental risk assessment, non-target organisms, surrogate species, tiered testing

**Abbreviations:** ERA, environmental risk assessment; GE, genetically engineered; GEIR, genetically engineered insect resistant; NTO, non-target organism

Most regulatory authorities require that developers of genetically engineered insect-resistant (GEIR) crops evaluate the potential for these crops to have adverse impacts on valued non-target organisms (NTOs), i.e., organisms not intended to be controlled by the trait. In many cases, impacts to NTOs are assessed using surrogate species, and it is critical that the data derived from surrogates accurately predict any adverse impacts likely to be observed from the use of the crop in the agricultural context. The key is to select surrogate species that best represent the valued NTOs in the location where the crop is going to be introduced, but this selection process poses numerous challenges for the developers of GE crops who will perform the tests, as well as for the ecologists and regulators who will interpret the test results. These issues were the subject of a conference “Surrogate Species Selection for Assessing Potential Adverse Environmental Impacts of Genetically Engineered Plants on Non-Target Organisms” convened by the Center for Environmental Risk Assessment, ILSI Research Foundation. This report summarizes the proceedings of the conference, including the presentations, discussions and the points of consensus agreed to by the participants.

## Introduction

According to 2012 data, GEIR crops were grown on approximately 170 million hectares globally, in 28 countries.<sup>1</sup> As a part of the larger environmental risk assessment (ERA) process, these

countries require that developers evaluate the potential for GEIR crops to have adverse impacts on valued NTOs. For regulators in countries considering the commercial planting of a GEIR crop, the analysis of NTO impact data and the application of that analysis to their particular circumstances, can be daunting. At the same time, conducting NTO testing poses numerous scientific, logistical and financial challenges for researchers, and these challenges are compounded when regulatory authorities require the generation of duplicative data generated in-country or data using local species, particularly when appropriate existing data from relevant geographies may be sufficient for an ERA of a GEIR crop.<sup>2</sup> Unfortunately, these challenges are likely to intensify as GEIR crops are considered for commercial planting in new countries.

These issues and their resolution were the subject of the conference “Surrogate Species Selection for Assessing Potential Adverse Environmental Impacts of Genetically Engineered Plants on Non-Target Organisms” convened by the Center for Environmental Risk Assessment (CERA), ILSI Research Foundation, June 26–28, 2012, in Washington, DC. The conference was one in an ongoing series that CERA has hosted on NTO issues. The objectives of the conference were

- To identify key criteria for surrogate species selection for laboratory, semi-field and field NTO testing and
- To identify best practices for surrogate testing, with a particular focus on facilitating data transportability.

## Assessing Non-target Impacts via Tier-Based Testing

Although the production of insect-resistant crops through genetic engineering is a relatively new technology, existing testing methods are available to assess the potential impacts of these crops on NTOs and to ensure their environmental safety.

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In essence, these crops bear transgenes that enable the plant to produce one or more pesticidal chemicals, for example, insecticidal Bt proteins, and researchers have decades of experience using tier-based testing to assess the effects of chemical pesticides on NTOs.<sup>2,3</sup> Four fundamental principles, developed and validated in the tier-based testing of chemical pesticides, have direct applicability to the testing of NTO impacts from GEIR plants:

- (1) Not all taxa with potential exposure to the pesticide need to be tested—testing a small fraction of representative taxa can effectively assess NTO impacts.
- (2) Tiered testing is an efficient approach to generate statistically robust data that accurately predict potential impacts from pesticides on NTOs.
- (3) Appropriately selected surrogate species can effectively represent NTOs when assessing potential impacts from chemical pesticides. Data generated using surrogates can be more consistent, of higher quality and of greater transferability than data generated using the NTO species themselves.
- (4) Results of tests using surrogate species can be extrapolated to predict and assess changes at the population, community and ecosystem levels.<sup>3</sup>

In a tier-based system for assessing chemical pesticide impacts, Tier 1 testing occurs under contained conditions in the laboratory or greenhouse and typically involves the exposure of a select group of representative species to levels of the pesticide many times higher than levels expected from environmental exposure, to ensure a sufficient margin of safety.<sup>2,4</sup> Provided there is an adequate margin of safety with lower tiers, testing at higher tiers, e.g., semi-field or field scale, is not required.<sup>5,6</sup> While semi-field and field scale assays are performed under more realistic conditions than laboratory tests, they are typically more complex, more difficult to standardize and have less statistical power than tests performed in the laboratory.<sup>4,7</sup>

For both chemical pesticides and insecticidal substances produced by GEIR crops, a fundamental challenge for the researcher is the selection of test species that will be used. It is obvious that not all species present in the receiving environment and potentially exposed to the GEIR crop-produced insecticidal substance can be tested. Conducting tests with actual NTOs expected to be exposed to the pesticide or GEIR crop may not be practical, economically feasible, or even legal, as in the case of endangered or protected species. (It has also been suggested that, in the context of risk assessment for biological control agents, the use of surrogates may be useful when a potentially impacted species is very rare.<sup>21</sup>) Tests are thus commonly conducted with relevant surrogate species that are most likely to be sensitive to the insecticidal protein, available in large numbers of consistent individuals and amenable to testing under confined conditions.<sup>8-10</sup> The selection of appropriate surrogate species for GEIR crops needs to result in the use of surrogate species that are predictive of potential impacts of the GEIR crop on NTOs in the field and thus will be protective of ecosystem structure and function.

As a result of decades of NTO testing with chemical pesticides, numerous surrogate species have been identified that

meet these criteria. Test results using these species have effectively assessed the environmental safety of chemical pesticides and informed regulatory decision making.<sup>11,12</sup> Many of these same species have also been used effectively in the assessment of potential impacts from GEIR crops. However, while there is considerable international harmonization regarding test guidelines for assessing impacts of chemical pesticides on NTOs,<sup>13,14</sup> guidelines for assessing GEIR crops vary from country to country.<sup>2</sup> For example, **Table 1** summarizes key features of the regulatory schema related to NTO assessments in six jurisdictions that have approved the use of GEIR crops.

Lack of consistency among regulatory jurisdictions can result in duplication of work and the inability to compare NTO test data developed in one country with those of another.<sup>2</sup> In addition, requirements for field tests, regardless of the results of lower tier testing or the requirement that a specific local species be included in NTO impact assessment studies can quickly escalate development costs for commercial production approvals. This disharmony could have a chilling effect on public sector scientists with limited research funding, who may be forced to collect NTO assessment data to meet the requirements of only a single regulatory program and forego a broader deployment of new GE varieties.

As more and more nations, representing a wider variety of agro-ecosystems, consider the adoption of GEIR crops, it is timely to re-evaluate the selection criteria for appropriate surrogate species for NTO testing. First, the establishment of an internationally harmonized approach to the identification and use of surrogate species would result in the recognition of numerous surrogates to serve as a “toolbox” from which researchers can select species as needed. Second, a harmonized approach would address the growing need for NTO test data to be transportable across national borders so as to reduce duplication of effort and associated costs both for regulators and for developers of new GEIR crops.<sup>6,15,16</sup>

## Surrogate Selection Criteria

Although surrogate species for lower Tier testing should be selected on a case-by-case basis for GEIRs, certain primary ecological functional groups should be considered when assessing GEIR crops, namely herbivores, pollinators, predators and parasitoids and decomposers. Probable routes of exposure should also be evaluated, and emphasis should be placed on species that either feed directly on the crop (one degree of separation) and on species that are predators or parasitoids of direct feeders (two degrees of separation). Testing species with more attenuated exposure to the crop is unnecessary from a risk assessment standpoint.<sup>7</sup>

The selection process for appropriate surrogates can be informed by existing databases of arthropod communities associated with major field crops.<sup>17,18</sup> These databases indicate substantially similar arthropod composition across crops. Herbivores comprise Lepidoptera, Coleoptera, Hemiptera and Diptera species; predators consist of Coleoptera, Diptera and Hemiptera species; parasitoids include the Hymenoptera, Diptera and Coleoptera; and decomposers are represented by Collembola,

**Table 1.** Comparison of Non-Target Organism Testing for GEIR Crops in Six Jurisdictions

	Argentina	Brazil	EU	Mexico	Philippines	United States
<b>Number of Bt events approved for unconfined release</b>	Maize: 9 Cotton: 1 Soybean: 1	Maize: 15 Cotton: 7 Soybean: 1	Maize: 1	Cotton: 2	Maize: 8	Maize: 10 Cotton: 7 Soybean: 1
<b>Field studies are required for each event or subset of events submitted for unconfined release</b>	Field studies to assess NTO are not required; the need for field studies is determined on a case-by-case basis.	Yes, field studies are required to assess NTO impacts, for each event to be submitted for commercial release.	Field studies are not required if (1) lower tier studies do not indicate negative effects and (2) lower tier studies were performed with plant material for one focal species per relevant functional group	Yes	Yes, data from local field studies are required.	No. This is determined based on a tiered testing scheme but may also be required for other reasons on a case-by-case basis.
<b>Tiered testing is addressed in regulations or guidelines</b>	No	Yes, in guidelines.	Yes, in guidelines.	No	Yes, in guidelines	Data requirements have been based on requirements for microbial pesticides, and additional data have been required where necessary.
<b>Standard Operating Procedures for NTO testing are addressed in regulations or guidelines</b>	No specific SOPs are provided in the regulations.	No specific SOPs are provided, but they are discussed in guidelines.	No SOPs are provided, but general requirements for testing are described in guidelines.	No	Applicant submits SOPs for approval. Tiered testing is discussed in guidance.	There are no official SOPs or guidelines published for plant-incorporated protectants*
<b>NTO species that must always be included in risk assessments</b>	No NTO species are required to be assessed.	No NTO species are required to be assessed.	No NTO species are required to be assessed.	None currently, but a list is being compiled	<i>Orius</i> sp., <i>Micraspis discolor</i> , <i>Chrysoperla carnea</i> , <i>Chilomenes sexmaculata</i>	Honey bees, Monarch butterflies in specific cases.
<b>NTO species that are typically included in risk assessments</b>	Species included are determined on a case-by-case basis.	<i>Doruluteipes</i> sp (Forficulidae: Dermaptera) and at least one Heteropteran are expected to be included.	Three or more NTO species (e.g., <i>Chrysoperla carnea</i> , lady beetle, parasitic wasp, carabid beetle, <i>Orius</i> sp), <i>Apis mellifera</i>	None currently, but a list is being compiled.	<i>Trichogramma</i> sp, <i>Apis</i> sp, <i>Coccinella septempunctata</i> , <i>Euborellia</i> sp, <i>Geocoris</i> sp, <i>Hypolimnas bolina</i> , <i>Selenopsis geminata</i> , carabid beetle, spider, braconid wasp	Northern bobwhite, rainbow trout or channel catfish, <i>Daphnia magna</i> , three or more nontarget insects (e.g., <i>Chrysoperla carnea</i> , lady beetle, parasitic wasp, carabid beetle, <i>Orius</i> sp), <i>Apis mellifera</i> .
<b>Data developed outside the country is used in NTO impact assessments</b>	Yes, if applicants demonstrate that for a particular trait and crop the risk hypothesis performed for NTO species in the Argentinean receiving environment can be assessed by the studies done in another country.	Yes, data developed outside can be used, however insects tested outside the country should be similar (e.g., same genera)	Yes, non-European species that represent species present in the European agro-ecosystems can be used in the NTO assessment, if justified.	Yes, on a case-by-case basis.	Yes, if data adheres to international protocols, guidelines and best practices.	Yes, as long as it meets USEPA standards.*
<b>Link to regulations</b>	<a href="http://64.76.123.202/site/agregado_valor/biotecnologia/60-SOLICITUDES/___experimental/index.php">http://64.76.123.202/site/agregado_valor/biotecnologia/60-SOLICITUDES/___experimental/index.php</a>	<a href="http://www.ctnbio.gov.br">http://www.ctnbio.gov.br</a>	<a href="http://www.efsa.europa.eu/en/efsajournal/doc/1877.pdf">http://www.efsa.europa.eu/en/efsajournal/doc/1877.pdf</a> <a href="http://www.efsa.europa.eu/en/efsajournal/doc/1879.pdf">http://www.efsa.europa.eu/en/efsajournal/doc/1879.pdf</a>	NA	<a href="http://biotech.da.gov.ph/Forms.php">http://biotech.da.gov.ph/Forms.php</a>	NA

\*See, e.g., reference 10.

Acarina, Diptera and Coleoptera. These taxa are most likely to be exposed to arthropod-active substances produced by the crop, and surrogates representing these taxa should be considered for NTO testing. Ideally, taxa chosen should be those commonly occurring in that crop, regardless of the geographic location, to enhance the transportability of the data collected.

Once the potentially impacted taxa are identified, surrogates for Tier 1 testing should be selected based on phylogenetic relatedness to the potentially impacted species, rather than on shared ecological function, e.g., if a crop pollinator may be negatively impacted by the crop, an appropriate surrogate would be a species closely related to the pollinator, regardless of the surrogate's ecological function.<sup>16</sup> When there is incomplete information regarding which species may be impacted by a particular pesticidal substance, surrogates should be selected to provide adequate taxonomic coverage to enable a confident prediction of no unacceptable adverse effects on NTOs.<sup>16</sup>

In addition to choosing surrogates for lower tier testing that accurately represent NTOs in the cropping system where the crop is going to be introduced, there are important practical considerations. Surrogates must be easily reared under controlled, standardized conditions to provide large numbers of consistent individuals having a high level of fitness; they must perform well on an artificial diet and be amenable to manipulation under laboratory conditions; and validated test protocols must be available that produce consistent, statistically robust data.<sup>8,19</sup>

The utility of surrogates decreases as one moves from semi-field to field scale testing. In these contexts, the emphasis should be on identifying representative taxa, a process that will also be informed by the arthropod community databases mentioned above.<sup>17</sup> Factors to consider in the selection process include results from lower-tier testing, routes of exposure, types and duration of exposure, the perceived importance of the organisms in the agro-ecosystem and their presence in sufficient numbers.<sup>20</sup>

## Conclusion

At the conclusion of the Conference, participants advanced the following points of consensus:

- (1) Surrogate species are the appropriate test organisms for laboratory and semi-field studies.
- (2) Representative taxonomic groups are the appropriate level of resolution (test unit) for census field studies.
- (3) Pests can be used as surrogates.
- (4) Measures of “surrogate” processes representative of ecological function in the field can be a valuable tool.
- (5) Identifying faunistic similarities across geographies supports data transportability.
- (6) Field studies should focus on the taxa that are one or two degrees of separation away from the crop.
- (7) Sufficient information for robust/rigorous risk characterization can be developed through problem formulation.
- (8) There was consensus on surrogate selection criteria for early tier tests.
- (9) Provided adequate margins of safety, hazard testing that is used to inform the in-field assessment informs the off-field assessment.

Moving forward, the development and validation of test protocols for new surrogate species will enlarge the toolbox, facilitating the selection of the most appropriate surrogates on a case-by-case basis. The identification of surrogate species that may be useful in the assessment of potential impacts on arthropod communities associated with major field crops in different geographies will contribute to the transportability of NTO assessment data collected in different regulatory jurisdictions.

### Disclosure of Potential Conflict of Interest

No potential conflict of interest was disclosed. Opinions and views expressed in the present article are strictly those of the authors and do not represent those of the organizations where the authors are currently employed.



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